REMARKS

Prior to the present submission, claims 20, 21, 87, 97-99, 106-113, 118, 128-130, 137-147, and 150-189 were pending in the application, with claims 108 and 139 withdrawn from consideration by the Examiner.

As an initial matter, Applicants note that the Disposition of Claims in the Office Action Summary appears incorrect, and request clarification of the status of the claims.

In the present submission, claims 97-99, 107, 109, 128-130, 138, 140, and 150-189 have been cancelled, and claims 20, 21, 87,106, 111, 113, 118, 137, 142, and 143, have been amended. Exemplary support for these amendments can be found in paragraphs [0100], [0115], [0122], and examples 8 and 40. No new matter is introduced by these amendments. Notwithstanding the foregoing, Applicants expressly reserve the right to prosecute subject matter no longer or not yet claimed in one or more applications that may claim priority to the present application.

Reconsideration of the claims is requested in view of the foregoing amendments and the following remarks.

1. 35 U.S.C. § 112, second paragraph

The rejection of claims 20, 21, 83-87, 97-107, 109-118, 128-138, 140-149, and 150-189 under 35 U.S.C. 35 U.S.C. § 112, second paragraph as allegedly failing to satisfy the definiteness requirement is respectfully traversed.

The rejection is premised on the assertion that the reference in the claims to "a genetic mutation that attenuates the ability of the bacterium to repair its midified nucleic acid to wild type" is allegedly unclear, and that a specific mutation must be included within the claim. Applicants strongly disagree that the claims as previously drawn are "insolubly ambiguous" (Honeywell Int'l, Inc. v. Int'l Trade Comm'n, 341 F.3d 1332, 1338–39 (Fed. Cir. 2003) (quoting Exxon Research & Eng'g Co. v. United States, 265 F.3d 1371, 1375 (Fed. Cir. 2001)), and submit that the claims as previously drawn reasonably apprise those skilled in the art of the scope of the claims.

Notwithstanding the foregoing, Applicants have amended claims 20 and 21 to refer to *Listeria* bacteria comprising one or more genetic mutations in *uvrA* and *uvrB* genes inhibiting excision repair of psoralen-induced interstrand crosslinks.

In view of the foregoing, Applicants request that the rejection be reconsidered and withdrawn.

A further rejection is premised on the assertion that claims 20 and 152 refer to "a method of treating or preventing any disease in a host yet the claims reads solely on the use of an L.monocytogenes bacterium. It does not appear that this bacterium could treat or prevent a disease other than one caused by L.monocytogenes." Office Action, page 3. Applicants submit that the rejection is based on an incorrect assertion.

The rejected claims are drawn to methods comprising the administration of *Listeria* bacteria. Vaccine compositions may be used to stimulate immunity (mediated by B-cells, T-cells, or both) to an antigen, and/or may be intended to stimulate the innate immune system, which comprises cells and mechanisms that defend the host in a non-specific manner. The innate system recognizes, and responds to, diseases in a generic way and does provide immediate short-term defense. It is well established that bacteria, including *Listeria*, stimulate the innate immune system, and can also be used to deliver foreign antigens to stimulate an immune response.

In this latter regard, Applicants have amended claims 20 and 21 to refer to *Listeria* bacteria comprising a nucleic acid sequence encoding a polypeptide heterologous to the bacterium operably linked to a promoter sequence directing expression of the heterologous polypeptide by the modified bacterium.

In view of the foregoing, Applicants request that the rejection be reconsidered and withdrawn.

A further rejection is premised on the assertion that claims 21 and 158 "do not make it clear whether or not [the antigen] is a heterologous antigen.... [or] that the bacterium has been modified so that it may not repair its modified nucleic acid." Office Action, page 3. With regard to the first part of this assertion, Applicants submit that the foregoing amendments render this rejection moot. It would appear that the latter part of this assertion is based on an incorrect understanding of the invention.

As described in some detail in the specification, psoralen-induced crosslinks affect the ability of the bacterium to reproduce, it is believed due to the termination of chromosome

replication. Such crosslinks, however, do not prevent the cell from transcription of genes and translation of the gene products into protein. Thus, whether or not "the bacterium has been modified so that it may not repair its modified nucleic acid" is immaterial, as this has no effect on the ability of the bacterium to express the antigen of interest. In the claimed bacteria, the modification of the microbial nucleic acid is such that proliferation is attenuated, while maintaining a sufficient level of microbial gene expression.

In view of the foregoing, Applicants request that the rejection be reconsidered and withdrawn.

Finally, a further rejection is premised on the assertion that the reference to "wild type" in the claims is unclear. Applicants submit that the foregoing amendments render this rejection moot.

2. 35 U.S.C. § 112, first paragraph

The rejection of claims 20, 21, 83-92, 95-107, 109-123, 127-138, and 140-149 under 35 U.S.C. 35 U.S.C. § 112, first paragraph as allegedly failing to satisfy the enablement requirement is respectfully traversed.

The Examiner has indicated that certain subject matter is enabled; specifically, methods of inducing an immune response to a heterologous antigen comprising administering an effective amount of a vaccine comprising an isolated, attenuated *Listeria monocytogenes* mutant with a deleted *uvrAB* gene which has been attenuated by treatment with psoralen S-59 and ultraviolet radiation, and equivalent methods of treating a disease in a host. Office Action, page 4.

Applicants submit that the skilled artisan would understand that the scope of enablement is not limited to "a deleted *uvrAB* gene" and "treatment with psoralen S-59."

The claims as amended herein refer to methods which utilize a bacterium comprising "psoralen-induced interstrand crosslinks introduced between the strands of genomic DNA double helix" and "one or more genetic mutations in *uvrA* and *uvrB* genes inhibiting excision repair" of interstrand crosslinks. The skilled artisan is taught that psoralen compounds may be used to induce intrastrand crosslinks into genomic DNA. As the skilled artisan was aware at the time the application was filed, this effect is not limited to psoralen S-59. *See, e.g.*, Greenberg *et al., J. Biol. Chem.* **276**: 31551-60 (2001).

Similarly, the skilled artisan is taught that genetic mutations may be introduced to block functional expression of the *uvrA* and *uvrB* genes. Introducing genetic mutations into the *uvrA* and *uvrB* genes in order to inhibit excision repair may practiced by introducing an in-frame stop codon or reading frame shift, or, as in the case of the examples provided in the specification, by deletion of the entire genes. Indeed, the specification's disclosure of deletion of the entire genes is sufficient to enable the claimed methods. Ex Parte Reinhold Holtkamp Sr., APPEAL 2007-4136, 2008 WL 1901981 ("as Appellant correctly points out, the law makes clear that the specification need teach only one mode of making and using a claimed invention. Engel Indus. Inc. v. Lockformer Co., 946 F.2d 1528, 1533 ... (Fed. Cir. 1991). See also Johns Hopkins Univ. v. Cellpro Inc. 152 F.3d 1342, 1361 (Fed. Cir. 1998) (holding that the enablement requirement is met if the description enables any mode of making and using the invention.); Amgen, Inc. v. Hoechst Marion Roussel, Inc., 126 F. Supp. 2d 69 ... (D. Mass. 2001) (holding that there is no requirement that the specification enable every mode for making and using the claimed products)).

Beyond this, the claims are directed to methods for preventing or treating a disease, and to methods for inducing an immune response, using a bacterium having one or more genetic mutations in *uvrA* and *uvrB* genes inhibiting excision repair. The structure of these genes was well known at the time the application was filed, including the identity of domains necessary for DNA binding, nucleotide binding, *etc. See, e.g.*, Swiss-Prot entry numbers Q8Y4F6 and Q8Y4F5. One of skill in the art would recognize that deletion of one or more of these domains would be sufficient to inhibit the excision repair function. Thus, introducing mutations in *uvrA* and *uvrB* genes that inhibit excision repair was well within the level of skill of the artisan. The Examiner refers on page 10 of the Office Action to Bowie *et al., Science* 247: 1306-10 (1990), which discusses in general terms the tolerance of protein sequences to amino acid substitutions, alleging that the skilled artisan would not know how to reduce gene product activity except by deletion of an entire gene. The fact, however, that certain general difficulties might be encountered in practice does not present a sufficient basis for rejecting a claim under the enablement requirement. *See, e.g.*, In re Chilowsky, 229 F.2d 457, 463 (CCPA 1956), Ex Parte Hicks, 2000 WL 33673734 at *3. Furthermore, the test of enablement is not whether any experimentation is necessary but whether, if experimentation is necessary, it is undue.

The rejection also asserts that the claims as previously written refer only to "nucleic acid targeted compounds" and to mutations that attenuate DNA repair without reference to specific genes. Applicants believe that the foregoing amendments to the claims, which refer to psoralen-induced crosslinks and to mutations in the *uvrA* and *uvrB* genes, adequately address these objections.

The rejection also asserts that the claims are drawn to "prevention" methods, which are allegedly not enabled because "there is no known HIV... [or] cancer prevention method or vaccine to date." Office Action, page 10. Respectfully, the rejection is based on nothing more than broad unsupported allegations that the disclosure is speculative coupled with various difficulties that might be encountered in practice. Again, such allegations do not present a sufficient basis for rejecting a claim under the enablement requirement. *See, e.g.*, In re Chilowsky, 229 F.2d 457, 463 (CCPA 1956), Ex Parte Hicks, 2000 WL 33673734 at *3. Applicants also question the relevance of what has been demonstrated "to date" without reference to the present specification. As stated in Chilowsky, "[t]he mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."

The rejected claims relate to vaccine compositions comprising *Listeria* bacteria. *Listeria* has a long history of use as a vaccine platform for both infectious and neoplastic diseases. *See, e.g.*, Ikonomidis *et al.*, Delivery of a Viral Antigen to the Class I Processing and Presentation Pathway by *Listeria monocytogenes*, *J. Exp. Med.* 180: 2209-18 (1994); Pan *et al.*, Regression of Established Tumors in Mice Mediated by the Oral Administration of a Recombinant *Listeria monocytogenes* Vaccine, *Cancer Res.* 55: 4776-79 (1995); Friedman *et al.*, Induction of Human Immunodeficiency Virus (HIV)-Specific CD8 T-Cell Responses by *Listeria monocytogenes* and a Hyperattenuated *Listeria* Strain Engineered To Express HIV Antigens, *J. Virol.* 74: 9987-93 (2000); Angelakopoulos *et al.*, Safety and Shedding of an Attenuated Strain of *Listeria monocytogenes* with a Deletion of actA/plcB in Adult Volunteers: a Dose Escalation Study of Oral Inoculation, *Infect. Immun.* 70: 3592-3601 (2002); Pardoll, Spinning Molecular Immunology into Successful Immunotherapy, Nature Rev. 2: 227- 38 (2002); Blattman *et al.*, Cancer Immunotherapy: A Treatment for the Masses, *Science* 305: 200-5 (2004); Lara-Tejero and Pamer, T-cell Responses to *Listeria monocytogenes*, *Curr. Opin. Microbiol.* 7: 45-50 (2004).

Applicants note that the Office Action acknowledges that the present specification provides adequate written description for methods of generating of an immune response to an antigen. The skilled artisan readily understands that such an immune response can be harnessed in a method to prevent disease. The immune response initiated by a vaccine may or may not ultimately be protective to the recipient; indeed, seronegativity following vaccination may be a problem even with common vaccines for diseases such as measles and varicella. The fact that vaccines may not be protective in any and all cases and for any and all diseases does not mean that the practice of such a method is somehow not enabled. Moreover, it is likely that most claims will encompass certain inoperable embodiments. For example, vaccines may also be unlikely to work if exposed to high temperatures or extremes of pH, as harsh conditions such as these are not particularly hospitable to biological materials. But, as the Board of Patent Appeals and Interferences has repeatedly pointed out in the context of enablement rejections, it is not the task of the claims to exclude such potentially inoperable embodiments. Atlas Powder Co. v. E.I. DuPont de Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984) ("Nor are we concerned that the claims may include inoperable embodiments, as is it not a function of the claims to specifically exclude possible inoperative embodiments").

Applicants respectfully submit that, when a proper enablement standard is applied, it is apparent that one skilled in the art could reasonably make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation. Because the enablement requirement demands no more, Applicants respectfully request that the rejection be reconsidered and withdrawn.

3. 35 U.S.C. § 112, first paragraph

The rejection of claims 20, 21, 83-92, 95-107, 109-123, 127-138, and 140-149 under 35 U.S.C. 35 U.S.C. § 112, first paragraph as allegedly failing to satisfy the written description requirement is respectfully traversed.

As in the rejection based on enablement, the written description rejection asserts that the claims as previously written refer only to "nucleic acid targeted compounds" and to mutations that attenuate DNA repair without reference to specific genes. Applicants believe that the foregoing amendments to the claims, which refer to psoralen-induced crosslinks and to mutations in the *uvrA* and *uvrB* genes, adequately address these objections.

The Office Action also asserts that "the specific mutation(s) of the polynucleotide sequence to accomplish decrease biological activity of the encoded polypeptide, is critical to the invention," again referring on pages 15 and 16 of the Office Action to Bowie *et al., Science* 247: 1306-10 (1990), which discusses in general terms the tolerance of protein sequences to amino acid substitutions.

Such assertions do not, however, support a conclusion that Applicants were not in possession of the claimed invention. The written description for a claim does not require a description of every possible means of practicing the claim. Adams v. U. S., 330 F.2d 622 (Ct.Cl.,1964) ("It is evident that this section does not require an inventor to disclose every possible way in which his invention may be used, nor does it limit the claims of the patent to the particular mode which the inventor considers best at the time of filing his application for patent"). Instead, the written description requirement is satisfied when the specification sets forth enough detail to allow a person of ordinary skill in the art to understand what is claimed and to recognize that the inventor invented what is claimed.

In the present case, Applicants are not claiming nucleic acids *per se*. As discussed above, the claims are directed to methods for preventing or treating a disease, and to methods for inducing an immune response. These methods include the use of a bacterium having one or more genetic mutations in *uvrA* and *uvrB* genes inhibiting excision repair. The structure of these genes was well known at the time the application was filed, including the identity of domains necessary for DNA

binding, nucleotide binding, *etc. See, e.g.*, Swiss-Prot entry numbers Q8Y4F6 and Q8Y4F5. And the specification provides examples of *uvrA* and *uvrB* deletion mutants, the use of which clearly fall within the scope of the claims. Whether or not other possible mutations could or could not also be used to practice the claimed methods is immaterial to the question of compliance with the written description requirement. What is material is that a person of ordinary skill in the art would readily acknowledge that Applicants invented what is presently claimed.

In the present case, the specification as filed adequately conveys to the skilled artisan that the inventor was in possession of the claimed invention as of the filing date. Because the written description requirement demands no more, Applicants request that the rejections be reconsidered and withdrawn.

CONCLUSION

Applicants respectfully submit that all rejections and objections have been obviated and that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (619) 203-3186.

Respectfully submitted,

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By: _____

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